May 8, 1952

Dear Jacques (and Mel):

I am sorry not to have taken time before to tell you how very much I enjoyed reading the papers you so kindly sent me in ms. The review is very stimulating indeed-- it seems to me for the first time to discard speculative superstitions about enzymatic "adaptation", and to discuss the experiments in factual terms. The kinetic analysis in cellular terms was especially valuable. I remember that during the few experiments that Roger and I did on the UV effects on Pseudomonas, it seemed as if it were the total yield rather than the rate of formation of adaptive enzyme that was primarily affected. Perhaps this can be most readily explained in terms of an all-or-none response of individual cells. Perhaps the terminology of neurophysiology would be as appropriate for enzyme studies as that of embryology!

I must confess that we have been essentially inert for the time being on lactase questions. This year has been rather difficult, with space problems, new people, and distractions from other interesting lines of work. Perhaps we should be discouraged by your findings on the identity of the lactases from diverse species, but I am still hoping to attack the possibility of specific differences among the variety of new fertile strains. Dr. Skaar has been working them up immunogenetically from a general viewpoint, and should soon be ready for a specific consideration of this particular antigen. I have also a great deal to do with the pestiferous details of the genetics of the Lac types. There is no question as to the correctness of the conclusions that you, for example, cited in your review, but it is a long way from an assurances of a diversity of genotypes to a detailed study of the loci from a genetic viewpoint. And I don't want to get too deeply into detailed physiological comparisons until the genetics is well worked out. I hope that we will soon be getting well into it again; meanwhile, Bonner and his students have been doing something on it, with no results discrepant with your own thinking.

On p. 49 there is a slight typographical error: lac_1^- should read lac_3^- in this case; I have taken the liberty of writing directly to the publisher myself in hopes it can be caught before the printing.

I cannot think of any important topic that your review did not discuss. Your treatment of accessibility of the enzyme foreshadows a very treacherous but unavoidable area for the future. You are probably already aware of the contradictions in the experiments on glycolysis by Lac_3^-. I have been very much concerned over the meaning of in vitro kinetic experiments with E. coli lactase, and have wondered whether the results do not reflect another enzyme system concerned with "transport". To change the subject only slightly, can one rephrase the problem of the relationship of enzyme-specificity to enzyme-forming-system-specificity in a slightly different way. Is any inductor incapable of reacting with (i.e. complexing) the enzyme, and vice versa. It is all very well to introduce the "organizer" concept (and I am in full sympathy with it, reserving, as you do, the greater qualitative control to the genotype), but still the inductor can only influence the cell metabolism by reacting with something, almost certainly not the enzyme itself. In terms of the ability to form

complexes, inducers and enzymes might be expected to share some specificity. Like yourself, however, I see no reason whybthis should be obligatory, except as it would be adaptive in an evolutionary sense. Because of a preoccupation with autocatalysts, too manyvwriters have forgotten that enzymatic adaptation is a mechanism, andevolved solution to a biological problem. It is this that we see for the most part, rather than the physiological necessities of the unique mechanism of protein synthesis.

I thank you also for the reprints recently received. A few of ours are in the mail, but we are waiting for the printing of the ones you will be most concerned about. May I ask whether you still have a copy of your descriptions of the bactogen? I have not yet seen this.

Esther asks to send her reggrds. She also sends (more tangibly) the enclosed ms. which is perhaps a little away from the focus of our joint interest, but more than a little relevant. It is the condideration of such complexities among the genes themselves that have made me despair of easy solutions and hypothesis of enzyme synthesis and gene action. It would be better if this inhibition did not operate: it tends to discourage the beginning experiments.

Have you been able to find any experimental substaatiation of a built-in inductor, especially in the constitutive stocks? I would be incline to guess against it, mostly on philosophical grounds, and partly on experimental failure (not pushed very far). There is also the lack of adaptation to galactose that one would expect, under certain conditions. Have you any information on adaptive specificity of galactozymase that would be useful as a "control" on this thought?

to in Paris

According third- or fourth-hand correspondence, skepticism is arising anew, as to the likelihood of a sexual basis of K-12 recombination. If or until the morphological or chemical bases of recombination are directly verified, we are likely to run in semantic circles, of which the issuenwill be dizziness, not clarity. If there is any impression that lambda is directly involved, I hope you may refer to my discussion of this with you some years ago in which I pointed out that lambda-free parents remained fully fertile, and this still holds more firmly than ever. There are indeed some very interesting new developments on genetic control of "sexual" compatibility which are opening new avenues of insight, but I hope that judgment can be reserved until all the facts are established. There are two stipulated findings that I cannot ignore: the inseparability of the agent of recombination in E. coli from the cell, and the occurrence of diploid hybrids heterozygous for each of the dozen differential markers of the parents. My 1949 paper on aberrant heterozygotes already pointed out some complexities, for example that Mal and S are usually deficient. It is possible that this deficiency is already present in the "gamete", and one can argue that this defect carried to its logical conclusion resembles an agent of transduction or transformation. There is a little evidence, however, that the elimination is post-meiotic (discussed in my CSH paper). We have fortunately had ample opportunity to compare K-12 with a transductive system in Salmonella, and the two systems are experimentally very different in every respect that would be associated with the difference in the recombination mechanism. Disregarding the details, the conceptual differences will be similar to those surrounding the interpretation of a spermatozoon Is it a parcel of biologically active, chemically isolable DNA, or is it a gamete with genetic properties defined so and so? The questions are not mutually exclusive, and we should be interested to answer both of them, according to the suitability of the experimental material.

Sincerely,

Joshua